

Comparative Studies on Coronary Dilators^{*1}

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The comparative potency of coronary dilators was investigated by using a rolling circular manometer system in the isolated perfused cat's heart. The doses capable of producing a 50 per cent increase in coronary blood flow were compared. The values in μ M for caffeine, Diuretin, Aminophylline, hydroxyethyl-theophylline, dihydroxypropyl-theophylline, adenosine, papaverine, and Persantin^{*3} were found to be 26, 28, 5, 50, 60, 0.0018, 3, and 2.5, respectively. The duration of action was evaluated by the doses required to maintain a 2-minute period of increased coronary flow. The values in μ M in the same order of the compounds mentioned above were represented as 52, 28, 5, 25, 5, 0.006, 5, and 0.13, respectively. The results derived from the experiments using coronary vascular strips suggest that a possible site of action of Persantin is located in the vascular smooth muscle itself.

Various experimental methods and materials have been used for the purpose of evaluating the potency of coronary dilators. In a previous paper from our laboratory, a method was described by NAKAZAWA et al. using a rolling circular manometer system in the isolated perfused cat's heart⁹⁾. This method was employed in the present experiments which deal with a comparative study on purine derivatives, papaverine and 2-6-bis-(diethanolamino)-4, 8-dipiperidino-pyrimido (5, 4-d) pyrimidine (Persantin).

Persantin was synthesized at the Scientific Department of the KARL THOMAE G. m. b. H. and its pharmacology was studied in detail by KADATZ²⁾. It is of interest to compare the effect of this new compound on coronary circulation with those of which clinical usefulness has been established.

METHODS

The isolated cat's heart was perfused with whole blood supplied by a normal donor animal anesthetized with sodium pentobarbital (Nembutal)

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^{*3} This compound was supplied by the Behringer Division of the Tanabe Co.

and heparinized. A rolling circular manometer was set between the donor and the isolated heart for measuring coronary inflow.

The following drugs were injected into the coronary circulation: caffeine and sodium benzoate, theophylline ethylenediamine (Aminophylline), theobromine and calcium salicylate (Diuretin), adenosine, papaverine HCl and Persantin. The doses were calculated as the bases of the compounds.

RESULTS

Purine derivatives

Injection of 2.5mg of xanthine into the coronary system failed to produce any change in coronary blood flow or cardiac contractions.

Caffeine and sodium benzoate enhanced the coronary blood flow accompanied by an augmentation of the amplitude of cardiac contraction. Theophylline ethylenediamine (Aminophylline) produced a more marked and prolonged increase in coronary flow than did caffeine. The duration of the augmentation of cardiac contraction initiated by Aminophylline was slightly longer than with caffeine. The percent increase of coronary flow was plotted against the concentration of the drug. As shown in Figure 1, the correlation between the effect of caffeine or Aminophylline and the dose of the drug was fitted by a straight line as a result of Chi-square test.

Theobromine and calcium salicylate (Diuretin) caused an increase in coronary flow with an initial transient decrease.

Hydroxyethyl- and dihydroxypropyl- theophylline produced a less prominent but more prolonged increase in coronary flow than caffeine or Aminophylline. The increased amplitude of cardiac contraction produced by hydroxyalkyl derivatives was much less marked than with caffeine or Aminophylline (Fig. 2).

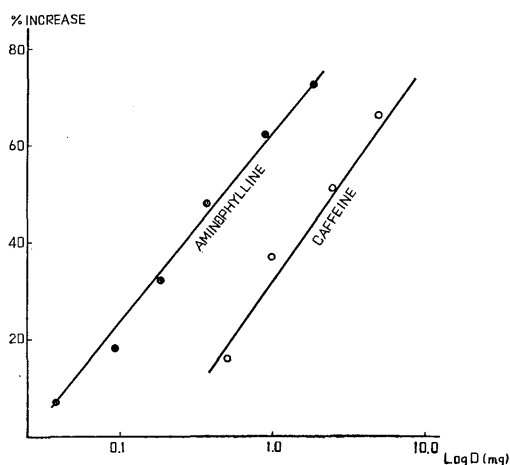
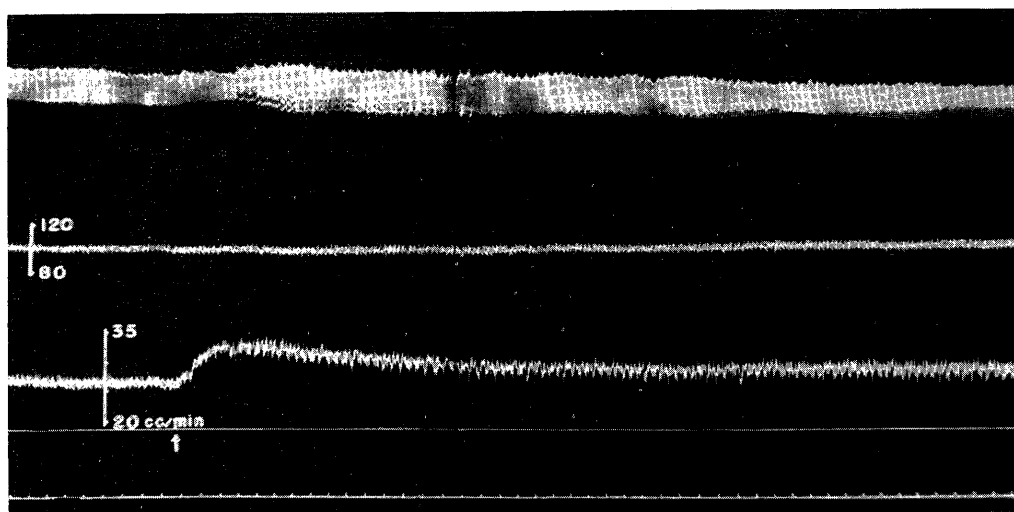


Fig 1. Relation between dose and effect of caffeine and Aminophylline.

Following the intra-coronary injection of adenosine there was observed a marked increase of flow. Adenosine was effective in a dose as small as 0.005mg. Cardiac contraction was not appreciably affected.

Papaverine

Papaverine produced a pronounced and lasting increase in coronary flow with dosages of 0.05 to 0.5 mg, the amplitude of heart contraction being slightly increased.



HC : Heart contractions
BP : Blood pressure
CBF : Coronary blood flow
Time marker, 6 sec.

Fig 2. Effect of 7.5 mg of Dihydroxypropyl-theophylline.

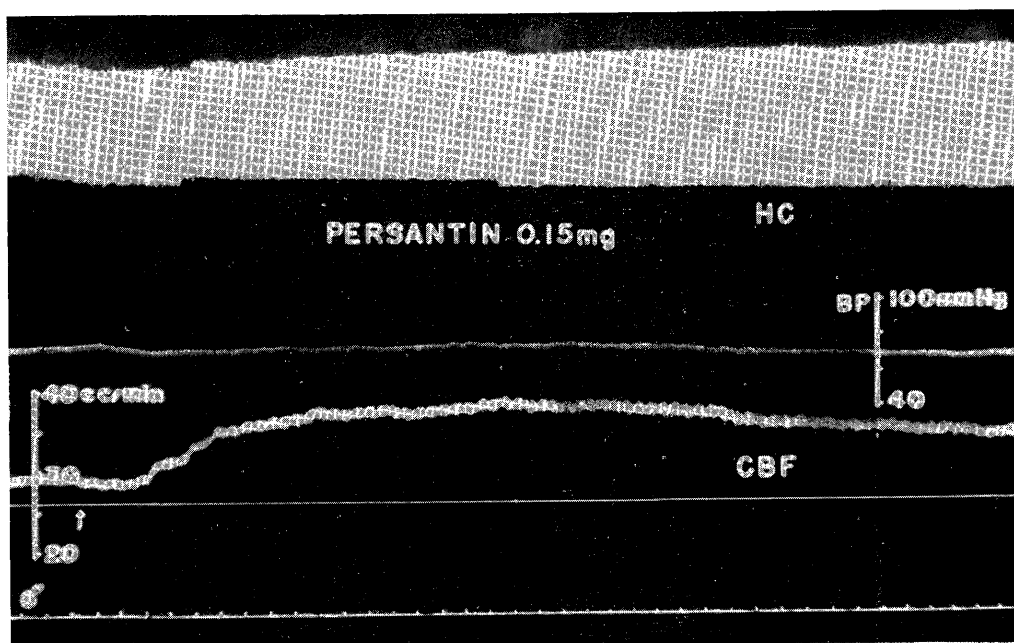


Fig 3. Effect of 0.15 mg of Persantin.

Persantin

A marked and prolonged increase in coronary flow was observed after the intra-coronary injection of Persantin (Fig. 3). The duration of the increased blood flow induced by 0.15 mg of the drug was 10 min. When 0.75 mg of Persantin was used the coronary flow did not return to the pre-injection level within 30 min. The amplitude of heart contraction was little changed by lower doses of Persantin but slightly enhanced by 0.5 mg and above. The increase in coronary flow and heart contraction elicited by Persantin was compared to that of Aminophylline. Figure 4 shows the correlation of the percent increase and doses of the two drugs. It was found that Persantin exerted less augmentation of

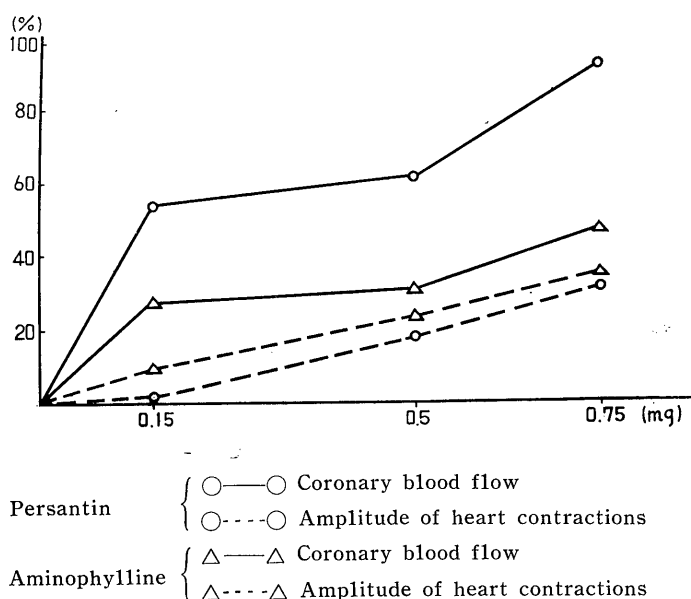


Fig. 4. Correlation of the percent increase and dose of Persantin and Aminophylline.

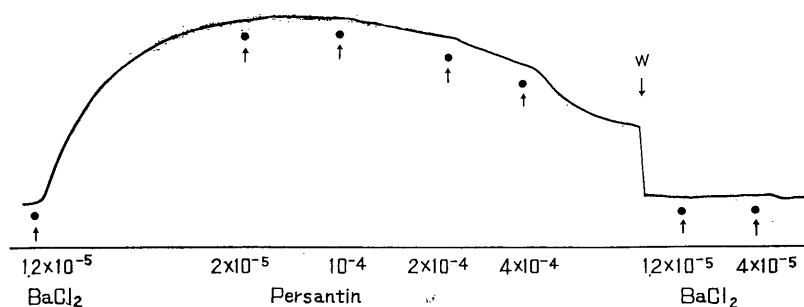


Fig. 5. Effects of BaCl_2 and Persantin on the coronary artery preparation.

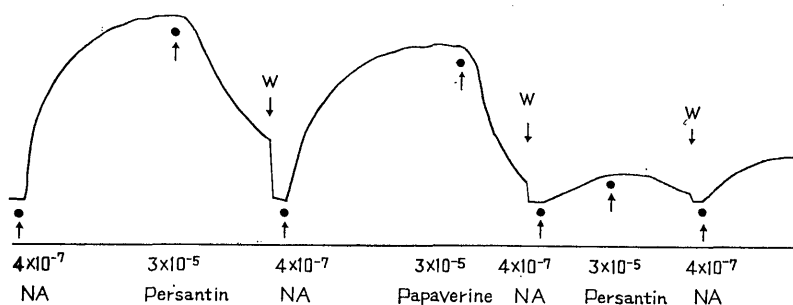


Fig 6. Effect of noradrenaline, Persantin and papaverine on the aortic strips.

heart contraction with doses producing approximately the same magnitude of increase in coronary flow as Aminophylline.

For the purpose of elucidating the site of action of Persantin the effect of the drug was investigated on preparations pig's coronary smooth muscle. The coronary artery was removed from the heart, cut spirally and suspended in a muscle chamber containing Tyrode solution bubbled with 95 per cent oxygen and 5 per cent CO_2 ⁴¹. The change in tension due to contraction or relaxation of the strips was recorded on a kymograph. When Persantin was added to the bath a significant relaxation was demonstrated in the strip which had been contracted by BaCl_2 . After 4×10^{-4} /cc of Persantin was applied the relaxed strip did not respond to BaCl_2 by contraction. Figure 5 shows the result of a typical experiment.

The spasmolytic effect of Persantin was compared with that of papaverine on cat's aortic strips by using the same experimental design as in the case of coronary muscle preparations. Persantin and papaverine elicited a relaxation of aortic strip of which the tonus had been increased by noradrenaline. After these relaxants were washed out and the bath fluid was changed an equivalent concentration of noradrenaline was applied. As can be seen in figure 6 the raised level of tonus produced by noradrenaline after Persantin was very much higher than after papaverine. This fact seems to indicate that the spasmolytic activity of Persantin on aortic smooth muscle is not so pronounced as that of papaverine.

DISCUSSION

Since LANGENDORFF's original design a measurement of coronary blood flow in the isolated perfused heart of various animals has been widely employed in the study of coronary circulation. In perfusing the isolated heart, it was found that whole blood was preferable to RINGER's solution in maintaining normal cardiac contractions and coronary blood flow during long experiments. As described by HEYMANN and KOCHMANN

the use of a donor animal made it possible to supply whole blood to an isolated heart as perfusing fluid. A rolling circular manometer system proved to be an appropriate apparatus for continuous recording of coronary blood flow.

The dose-response relationships for caffeine and Aminophylline in producing an increase of coronary flow was fitted by a straight line by the Chi-square test. On this basis the doses required to give a 50 per cent increase of flow were compared. The comparison of the durations of action was based on the assumption that the period of increased blood flow would be directly proportional to the doses employed.

The present findings (Table 1) indicate that caffeine and Diuretin possess a moderate coronary vasodilator potency with a short duration of action. Aminophylline appears to be equipotent with papaverine in providing a maximal increase of coronary blood flow as well as in the duration of vasodilatation. Hydroxyethyl-theophylline and dihydroxypropyl-theophylline are less potent than the above drugs but seem to be long acting coronary vasodilator agents with less marked augmentation of amplitude of cardiac contraction. Adenosine is the most potent coronary vasodilator among the compounds tested.

DAWEKE and BECKER¹⁾ demonstrated the comparative effectiveness of some xanthine derivatives by using isolated perfused guinea pig heart. The doses of caffeine, theobromine (Diuretin), Aminophylline (theophylline) and hydroxyethyl-theophylline required to produce about a 50 per cent increase of the coronary flow are larger in our experiments than the values reported by these investigators. This fact may be due to differences in heart weight different experimental animals.

A coronary vasodilator for therapeutic use should be a compound capable of supplying more oxygen to the myocardium than the increased oxygen demand required by the augmentation of cardiac work induced by the drug employed. Although oxygen consumption was not determined in the present study, caffeine, Diuretin and Aminophylline seem to increase the work load of the heart as a result of an augmentation of cardiac contractions. Persantin and papaverine did not cause a pronounced

Table I.
Comparison of the potency
of coronary vasodilators.

Drugs	Dose (μ M)	
	A	B
Diuretin	28	28
Aminophylline	5	5
Hydroxyethyl-theophylline	50	25
Dihydroxy-propyltheophylline	60	5
Caffeine	26	52
Adenosine	0.0018	0.006
Papaverine	3	5
Persantin	2.5	<0.13

A ; Dose required to produce a 50% increase in flow

B ; Dose required to maintain a 2 minutes period of increased flow.

increase of cardiac contractions. KADATZ²⁾ has reported that Persantin did not increase the oxygen consumption of heart muscle. In our experiments Persantin showed coronary vasodilatation approximately equipotent with papaverine in producing a peak increase of flow. The duration of effect of Persantin is much more prolonged than papaverine when compared on a molar weight basis.

Evidence has been presented by KADATZ²⁾ that the main site of action of Persantin is peripheral. In our present work, Persantin induced a relaxation of isolated coronary strips which had been constricted by BaCl₂ and furthermore, after the administration of the former the strip did not respond to the latter by constriction. These findings may suggest that the site of action of Persantin is located the vascular smooth muscle itself.

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